REMARKS

I. Disposition Of Claims

By this amendment, Applicant has canceled Claims 1-4, and 6-34, prior to further examination of this application, in order to protect a commercial embodiment, namely, an immunogenic composition comprising a lipooligosaccharide (LOS) isolated from *Moraxella catarrhalis* and detoxified by treating to remove esterified fatty acids to produce detoxified LOS (dLOS) and an immunogenic carrier covalently linked thereto, and, thus, for reasons unrelated to patentability. Claims 39-47 are pending. Thus, Claims 39-47 are presented for consideration. Reexamination and reconsideration of the application are respectfully requested.

II. Submission of Drawing

Enclosed for *re-filing* are three (3) sheets for formal drawings.

III. Patentability Over Citations

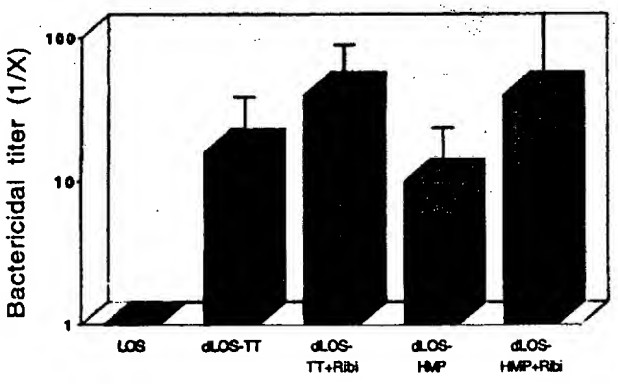
The Office Action rejected the claims under 35 USC 103(a) as being unpatentable over Vaneechoutte et al., Journal of Clinical Microbiology 28:182, 1990, in light of Gu et al., U.S. Patent Number 6,207,157, and Campagnari et al., Microbial Pathogenesis 8:353, 1990. Vaneechoutte et al. describes antibody-reactive compositions comprising lipooligosaccharides isolated from *Moraxella (Branhamella) catarrahlis.* Gu et al. describes a conjugate vaccine for nontypeable *Haemophilus influenzae* comprising lipooligosaccharide (LOS) from which esterified fatty acids have been removed conjugated to an immunogenic carrier. Campagnari et al. shows that lipooligosaccharide epitopes are shared among Gram-negative non-enteric mucosal pathogens, examples of which *include M. catarrahlis* and *H. influenzae.* It is the Office's contention that the combination of these references would make the development of the instant invention obvious to one skilled in the art.

According to the MPEP 2143:

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Additionally, MPEP 716.02(a) states that "Greater than expected results are evidence of non-obviousness." In light of these criteria, the Applicant makes three arguments for the non-obviousness of the instant invention.

First, the invention shows unexpectedly superior results than those reported in the art. Neither Vaneechoutte et al. nor Campagnari et al. provided evidence that LOS obtained following their methods would induce bactericidal activity of immune antisera against *M. catarrhalis*. In contrast, the patent specification shows in Figure 1 (reproduced below) that dLOS conjugates obtained following the proprietary method would indeed induce bactericidal activity of immune antisera against *M. catarrhalis*. Figure 1 also shows that dLOS conjugates are dramatically more effective than LOS (as would be obtained following the methods of Vaneechoutte et al. and Campagnari et al.) in inducing bactericidal activity of immune antisera against *M. catarrhalis*. These side-by-side comparisons confirm greater than expected results.



Second, the immunogenicity of detoxified LOS is unpredictable, which is repeatedly taught in the art. Gupta et al., I&I 60: 3201, 1992, of record, shows that LPS isolated from *V. cholerae*, detoxified by alkaline treatment with hydrazine, and conjugated to a carrier protein results in a conjugate that raises bactericidal antibodies, i.e., is potentially a vaccine. Polotsky et al., I&I 62: 210, 1994, of record, describes LPS isolated from *S. flexneri* and detoxified by treatment with either acetic acid producing O-SP (to cleave lipid A from the OS) or with hydrazine producing deALPs (to remove primary O-linked fatty acids), and shows that coupling to a carrier protein results in both conjugates being immunogenic and raising bactericidal antibodies. However, the O-SP conjugates were more immunogenic. Moreover, these experts state at the last sentence, "These experimental data indicate that it is not yet possible to predict the immunogenicity of the saccharide component of newly devised conjugates by measurement of its molecular weight or by its ratio to protein." This last sentence means that a leading group in the field cannot tell whether acid or hydrazine treatment will result in a detoxified LOS or LPS that retains its immunogenicity. Konudu et al., I&I 62: 5048, 1994, of record, shows *E. coli* O157 LPS being detoxified by acid treatment or by hydrazine treatment, both conjugates raising similar levels of bactericidal antibodies, with the acid treated conjugates being slightly although not statistically better. Gupta et al., I&I 63: 2805, 1995, of record, compares different routes of detoxification of *E. coli* O111 LPS, in this case hydrazine detoxification and the use of an adipic dihydrazide linker giving the best results. Again, the same experts, at the bottom of the left column of page 2809, state: "It is not yet possible to predict the immunogenicity of the saccharide component by in vitro methods, so it will be necessary to compare the immunogenicity analyses of new conjugates." In other words, retaining immunogenicity while reducing toxicity is experimental. Finally, Konadu et al., I&I 64: 2709, 1996, of record, compares acid and hydrazine detoxification of LPS from *S. paratyphi* A, and shows that hydrazine treatment results in conjugates that do not raise bactericidal antibodies, while acid treatment does. In sum,

this body of work shows that the contribution of detoxification to immunogenicity cannot be predicted in advance. Consequently, this showing negates any reasonable expectation of success in Applicant's treatment of LOS. *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (Obviousness under § 103 requires "a reasonable expectation of success."). Applicants' success in detoxifying the LOS from *M. catarrhalis* while retaining its immunogenicity was empirical and nonobvious.

Third, there is no suggestion in the art to select Applicant's treatment of LOS. The Office cited Campagnari et al. as showing that LOS epitopes are shared among Gram-negative non-enteric mucosal pathogens, which include *H. influenzae* and *M. catarrahlis*. However, Campagnari et al. in no way teaches that the epitopes remaining after detoxification of LOS would be shared. To the contrary, past attempts to remove esterified fatty acids had shown that the contribution to immunogenicity of such deacylation could not be predicted in advance. Erwin et al., I&I 59: 1881, 1991, of record, studied the impact of enzyme deacylation on the bioactivities of several LPS materials. The enzymatically deacylated LPS from *E. coli, H. influenzae, N. meningtidis,* and *S. typhimurium* were similarly reduced in potency in the *Limulus* toxicity test, 30- to 60-fold reduction in potency relative to the corresponding mock-treated LPS (p. 1883, col. 1, ¶ 1). However, while the mitogenicity of enzymatically deacylated LPS from *E. coli, H. influenzae,* and *S. typhimurium* was reduced 15-fold, the mitogenicity of *Neisseria* LPS was reduced 100-fold by enzyme deacylation (p. 1883, col. 1, ¶ 2). This incongruity caused Erwin et al. to hypothesize that deacylation could lead to different structural alterations for one LPS compared to another LPS (p. 1885, col. 1, ¶ 2). Erwin et al. reasoned that deacylation might result in a conformational change in the LPS. *Id.* Because the binding of antibodies is conformationally dependent, this possibility caused Erwin et al. to posit that deacylation might block immunogenicity. *Id.* The conclusion from Erwin et al. is that the contribution of deacylation to the bioactivity of a given LPS cannot be predicted with confidence from the reported structure-activity relationships of lipid A or from the behavior of other deacylated LPS (abstract, last line; p. 1884, col. 2, ¶ 1; p. 1886, col. 1, ¶ 2). Accordingly, there is no reason or suggestion in the art to select

Applicant's treatment of LOS, deacylation, when the art of Erwin et al. indicates that it was uncertain whether it could have been used successfully. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed Cir. 1988) ("There must be a reason or suggestion in the prior art for selecting the procedure used.")

Based on these three points, it is clear that the instant invention is not obvious and rejection of the pending claims should be withdrawn.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

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